REMARKS

The final Office Action mailed June 18, 2008, has been received and reviewed. All claims stand objected to or rejected. New claims 36 and 37 are presented herein. Basis for new claims 36 and 37 can be found throughout the Specification, and more specifically at paragraphs [0012] and [0033], and original claims 4 and 32.

The application is to be amended as previously set forth. No new matter has been added. Reconsideration is respectfully requested.

35 U.S.C. § 103 Obviousness Rejections

Obviousness Rejections Based on Cassol *et al.*, *Journal of Clinical Microbiology*, 1997, 35(11):2795-2801 in view of Cassol, *et al.*, *Mem. Inst. Oswaldo Cruz, Rio de Janeiro*, 1996, 91(3):351-358) and U.S. Patent 5,482,834 to Gillespie

Claims 2 through 4, 6, 7, and 17 are rejected under 35 U.S.C. § 103(a) as allegedly being made obvious by Cassol *et al.*, *Journal of Clinical Microbiology*, 1997, 35(11):2795-2801 (hereinafter "Cassol 1997") in view of Cassol, *et al.*, *Mem. Inst. Oswaldo Cruz, Rio de Janeiro*, 1996, 91(3):351-358) (hereinafter "Cassol 1996") and U.S. Patent 5,482,834 to Gillespie (hereinafter "Gillespie"). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, the Examiner must determine whether there is "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007). While the references need not teach or suggest all of the claimed limitations, the Office must explain why the differences between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. *Id.*

A *prima facie* case of obviousness under 35 U.S.C. § 103(a) has not been established because there is no reason that one of ordinary skill in the art would have been prompted to combine the applied references in the manner asserted by the Office and because the combination of applied references actually teaches away from the presently claimed method. In addition, the

results of the presently claimed method would have been unexpected.

It is respectfully submitted that, without the benefit of hindsight, there would have been no reason in the applied references, common knowledge, or the nature of the problem itself that would have prompted a person of ordinary skill in the art to combine the applied references in the manner asserted in the Office Action. Cassol 1997 is concerned with quantification of HIV RNA whereas Cassol 1996 only concerns sequencing and genetic characterization of HIV RNA. This is emphasized in Cassol 1997, which provides the following:

> "Since first introduced for the detection of HIV-1 DNA in 1991 (2), PCR-based dried blood spot methods have proven particularly effective for the early diagnosis of neonatal infection in developing and developed countries (4,9,10,29) and for monitoring the emergence of drug resistance mutations (7), characterizing the genotype of transmitted virus (7), and tracking the global spread of HIV-1 subtypes (5). (Emphasis added)."

See Cassol 1997 at page 2795, second column.

It is noted that reference (7), referred to in the above citation, is Cassol 1996. Hence, Cassol 1997 states that dried blood spots had been used before, but only for non-quantitative research. It is acknowledged in Cassol 1997 that the article teaches a different use of dried blood spots than previously described methods. Specifically, Cassol 1997 states that "we describe here the extension of filter paper-based methods to the quantification of viral RNA in dried plasma spots (DPSs) (emphasis added)." Accordingly, Cassol 1997 teaches that their research provides a novel use of dried blood spots. It is respectfully submitted that the novel use of dried blood spots in a quantification method for viral RNA would not have been obvious in view of previously described methods, such as those of Cassol 1996.

It is further submitted that one of ordinary skill in the art would not have been motivated to combine the teachings of Cassol 1997 and Cassol 1996 because Cassol 1997 concerns quantification, whereas Cassol 1996 concerns sequencing and genetic characterization of HIV. As is known in the art, and set forth in the applied references, methods of sequencing RNA, such as the method of Cassol 1996, require markedly different conditions than methods of quantifying RNA, such as the method of Cassol 1997. It is known in the art that, when total RNA is quantified, essentially the total amount of RNA in a sample must remains intact. This, however, is not necessary in methods of sequencing RNA. Instead, much of the RNA is allowed to be

degraded during the process so long as sufficient RNA remains in the sample to enable sequencing. Based on these distinct differences, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to combine such different applications of dried blood spots.

As acknowledged by the Examiner, Cassol 1997 does not teach a process for quantifying a total amount of nucleic acid in a 100 microliter sample. *See* Office Action of June 18, 2008, page 4. Rather, Cassol teaches using 50 microliter samples. The Examiner states that "it would have been obvious to detect total HIV-1 RNA, as taught by Cassol 1997, using similar methods of the Cassol 1996 reference." *Id.* at page 5. At the priority date of the present invention, it was commonly taught in the art that only small volumes were suitable for quantification purposes. The art teaches against the use of large volumes of sample on a solid carrier for quantifying nucleic acid. As provided in paragraph [0015] of the as-filed specification, high amounts of sample were not considered suitable for quantification because of observed inhibitory effects. This is illustrated by the fact that Cassol 1997 teaches that the volume of the HIV Quantification Standard is reduced from 100 to 25 µl in order to compensate for the smaller 50-µl volume of dried plasma spot specimens. *See* Cassol 1997, page 2796, ¶3. Accordingly, based on the perception in the art that the use of large volumes was disadvantageous in quantification methods, the method of Cassol 1997 was specifically adapted to use smaller volume dried plasma spots.

Cassol 1997 further emphasizes the use of small input samples (e.g., 50 µL) for dried plasma spots stating that "[q]uantification of RNA levels with DPSs will be particularly valuable in the neonatal setting, in which only minute amounts of sample are available." *Id.* at page 2800, lines 25-27. This further demonstrates that one of ordinary skill in the art would not have had a reasonable expectation of success in using larger volume dried plasma spot samples for quantification purposes at the time of the present invention. By discouraging the use of large volume samples, Cassol 1997 teaches away from the present invention.

In the Office Action, it is asserted that Cassol 1997 does not preclude the use of larger sample sizes generally. *See* Office Action, page 5. It is noted that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551,

553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that the combination is more likely to be nonobvious). Cassol 1997 teaches that amplification reactions may become saturated when using a sample having a large volume (i.e., 200-μl). *See* page 2799. Thus, the closest reference applied in the Office Action (i.e., Cassol 1997) suggests that using a large volume sample would potentially render the method inoperable due to saturation of the amplification reactions. It is, therefore, respectfully submitted that one of ordinary skill would have been led away from the method of claim 1 based on the teachings of Cassol 1997. It is further submitted that, because it was known in the art that using large volume samples caused undesirable saturation of amplification reactions, one of ordinary skill in the art would have found the results of the claimed method surprising or unexpected.

Based on the uncertainty of success in using a large volume sample in a method of quantifying a nucleic acid, the results of using a large volume sample would not have been predictable to one of ordinary skill in the art. In the Office Action, it is alleged that "given the finite number of choices (50 or 2000 microliters) that are both known to have predictable results (quantification of HIV-1 RNA, total RNA of interest), the invention as a whole would have been obvious." Office Action, page 4. The fact that Cassol 1996 teaches using 2000 microliter dried plasma spots in a method of sequencing RNA, does not detract from the teachings in the art and in Cassol 1997 against the use of large volumes for quantification of the amount of nucleic acid. In view of such teachings, one of ordinary skill in the art would not have been led to select a large volume sample for use in a method of quantifying a total amount of HIV nucleic acid.

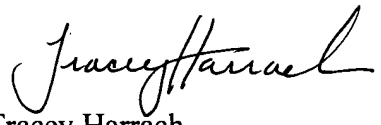
It is further asserted that one of ordinary skill in the art would have needed some reason to select among the several, unpredictable alternatives to arrive at the method of claim 1. *KSR* at 1740-1741. However, no explanation has been given by the Office why it would have been obvious to one of ordinary skill in the art to use a 100 microliter sample in a process for quantifying a total amount of HIV nucleic acid. According to the Office, the 2000 microliter spot of Cassol 1996 was adequate for quantifying a particular HIV nucleic acid of interest. *See* Office Action, page 3. Cassol 1996, however, teaches only semi-quantitative detection of HIV drug-resistance mutations. This means that a ratio between HIV drug-resistance mutations and non-resistant mutations was determined. Therefore, a relative amount of HIV drug-resistance

mutations in relation to an amount of non-resistant mutations is determined, but an absolute nucleic acid amount remains unknown. In the experiments of Cassol 1996, different conditions are required as compared to a total RNA quantification experiment. In determining such a ratio between nucleic acids, the nucleic acids may be degraded during the experiment as long as the ratio between the nucleic acids remains the same. In contrast, when total RNA is quantified, it is a prerequisite that essentially the total amount of RNA in a sample remains intact. Thus, one of ordinary skill in the art would not have been motivated to combine the method of sequencing of Cassol 1996 with the method of quantification of Cassol 1997.

It is further alleged in the Office Action that "Cassol 1997 discloses previous results with larger input sample sizes of 200 µl (page 2799)." Office Action, page 5. The 200 microliter samples of Cassol 1997 are, however, not dried plasma spots, but rather unspotted liquid plasma samples. Specifically, Cassol 1997 teaches if 200 µl samples are taken for quantification, they are not spotted on a solid carrier but directly used in a quantification experiment. Specifically, Cassol 1997 teaches that "[i]n initial experiments, to serve as reference standards, RNA was extracted from 200 µl aliquots of the remaining (unspotted) plasma, and the RNA was amplified in parallel (emphasis added)." Cassol 1997 at page 2796, first column. Cassol 1997 teaches using unspotted liquid 200 µl plasma samples to amplify RNA as a reference standard, but does not teach using a larger sample size a administering at least 100 microliters of the at least one sample to a piece of filter paper capable of absorbing the at least one sample, wherein the absorption results in at least one spot of the at least one sample on the filter paper. It is, therefore, respectfully submitted that *ex post* reasoning has been used in reading the teachings of the as-filed specification into the applied references.

The application should now be in condition for allowance. If, however, questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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